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What is This?
A systematic review of combination step III opioid therapy in cancer pain: An EPCRC opioid guideline project

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Abstract

Background: The use of combinations of opioids is a common clinical practice; however, this is not advocated by the World Health Organization (WHO) analgesic ladder. As opioid combination therapy becomes used increasingly, a review of the evidence on this practice was conducted.

Aims: To carry out a systematic review of the use of strong opioids in combination in cancer pain.

Methods: The following databases were searched electronically: Embase (1980–2010 week 2), Medline (1950–2010 week 1) and the Cochrane Database of Systematic Reviews (fourth quarter 2009). Only strong opioids as defined by the WHO ladder and full opioid agonists were examined. Only studies conducted in human, adult patients with chronic cancer pain were eligible. Studies must have contained data on efficacy and/or side effects in the key point. Appraisal was conducted using predetermined criteria set by the EAPC guideline development group. All potential papers were reviewed independently by both authors.

Results: In total 596 articles were retrieved resulting in only two eligible studies, which were rated as grade C and grade D evidence. These examined morphine in combination with oxycodone or fentanyl/methadone.

Conclusion: Only a weak recommendation can be used to support combination opioid therapy. This recommendation is also based on the caveat that the desirable effects of combination opioid therapy is outweighed by any disadvantages that this would confer. Prospective randomized trials are needed to clarify the benefits and safety of combination opioid therapy.

Keywords

Neoplasm, pain, opioids, opioid combination

Introduction

Multiple opioid receptors were first demonstrated through pharmacological means (antagonists) in the 1960s and 1970s.1 Opioids have, however, been used as the mainstay of analgesia long before this and continue this way. In cancer, pain is one of the most common symptoms2 and strong opioids remain at the centre of our cancer pain armamentarium.

Use of a single strong opioid in cancer pain management has been common practice for decades; however, it is evident that opioid prescribing practice is in a degree of metamorphosis. Patients often respond differently to one opioid over another, and this is the rationale for opioid switching. When opioids are switched, analgesia is often achieved at doses lower than equianalgesic dose conversions would suggest necessary.3 This is taken in the context of mean/median values, so there can be a variation. While a systematic review has concluded that the evidence to support this practice is limited,4 in recent years evidence has been evolving.5 Switching from one opioid to another is now accepted as part of standard practice in certain clinical situations.

Using two strong opioids simultaneously, so called “combination opioid therapy”, is another practice that
has become more commonplace. The rationale for combination opioid therapy is to:

- Improve analgesia
- Limit the development of opioid tolerance
- Decrease opioid side effects by using opioids which together have a lesser effect on mu opioid receptors than individually (reducing nausea, constipation, respiratory depression).

In the clinic there can be practical reasons why strong opioids are used in combination. Fast-acting fentanyl preparations are sometimes used to manage breakthrough cancer pain while another strong opioid is used to provide background pain control.

Although opioids are sometimes combined in the clinical setting, the use of opioid combinations is not advocated by the World Health Organization (WHO) analgesic ladder for cancer pain relief. At its conception, the aims of the WHO ladder were to encourage clear prescribing and appropriate titration of analgesia (on the background of a limited opioid armamentarium at step 3) which could be adopted on a worldwide basis. Combination opioid therapy was not addressed at this time.

The rationale behind opioid switching and combination opioid therapy overlaps and has become more robust as our understanding of the basic science has developed. Three major groups of opioid receptors have been identified; mu opioid peptide (MOP), kappa opioid peptide (KOP) and delta opioid peptide (DOP). In opioid switching, when an opioid acting at the MOP receptor is switched to another MOP receptor agonist, analgesia is often attained at lower doses. This suggests that incomplete cross-tolerance exists between opioids and differences exist between opioids that act at MOP receptors. This would contribute to the inherent differences between opioids when used at equivalent doses. Pharmacokinetic and pharmacodynamic factors, both influenced by pharmacogenomics, are clearly also important, for example individuals with dysfunctional CYP2D6 (part of cytochrome p450) have impaired ability to metabolize codeine, which is the prodrug of morphine.

As opioid combination therapy becomes increasingly used, a review of the literature supporting this practice would seem appropriate. The European Association of Palliative Care (EAPC) recommendations on opioids in cancer pain have identified the practice of combination opioid therapy as an important area. A systematic review, literature appraisal and recommendations for combination of opioid therapy have been conducted.

The systematic review assessed patients with cancer, on strong opioid analgesia in which two or more strong opioids were used simultaneously and analgesia and/or side effects were assessed as study outcomes.

Methods

Ethical approval was not required for this systematic review. The literature search was completed using recommendations from the EAPC guideline development group. The following databases were searched electronically: Embase (1980–2010 week 2), Medline (1950–2010 week 1) and the Cochrane Database of Systematic Reviews (4th quarter 2009). The date of the last literature search was 26 January 2010.

The following key words were used as search terms: “opioid synergy” and “opioid combination”. A search was also undertaken when two or more of the following key words appeared in the title (“morphine”, “oxycodeone”, “hydromorphone”, “fentanyl” and “methadone” using MeSH terms and including all subheadings).

Inclusion criteria

Studies included had to:

- Be conducted in human, adult patients
- Include strong opioids (as defined by the WHO ladder and full opioid agonists were examined) administered by any route
- Be written in English
- Research chronic cancer pain
- Examine data and efficacy and/or side effects
- Refer to two strong opioids administered simultaneously
- Follow any study design type (only crossover studies where simultaneous use of two opioids occurred were eligible).

Exclusion criteria

Studies meeting any of the following were excluded:

- Combination opioids used in the peri-operative setting (including patients undergoing cancer surgery)
- Studies which examined short acting fentanyl preparations for breakthrough pain in combination with other strong opioids, were not included
- Buprenorphine was excluded (partial agonist).

Meta-analyses were eligible; however, where narrative reviews were obtained (review articles where a clear
methodology of literature searching and appraisal was not recorded), all references cited were appraised.

**Appraisal**

The broad search strategy adopted meant a large number of potential papers were identified. All titles were reviewed by one of the authors (BL) and the abstracts of all potentially relevant articles were examined. Following this, potentially relevant articles were reviewed independently (BL, MF) and appraised. Appraisal was conducted using predetermined criteria set by the EAPC guideline development group (Appendix 1). All outcomes were considered. Following this, key points were graded according to the supporting evidence (Appendix 2). A recommendation statement for each key point was then developed.

**Results**

In total, 596 articles were retrieved following the literature search (Figure 1 – literature search). These were reviewed by one author (BL) and, if of potential relevance, the abstracts were examined. Some 80 abstracts were read, of which 71 were discarded. Nine articles were reviewed and this resulted in two articles which were eligible. These were critically appraised by both authors. The excluded studies are shown in Table 1.

The two included articles examined combination opioid therapy in cancer pain. These are as follows:

- Lauretti GR, Oliveira GM, Pereira NL. Comparison of sustained-release morphine with sustained-release oxycodone in advanced cancer patients.16

Lauretti et al. evaluated variable doses of both sustained-release oral morphine and sustained-release oxycodone in a crossover study of 22 patients with advanced cancer. The primary aim of this study was to evaluate the analgesic profile of the combination of

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**Table 1. Excluded studies**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Design</th>
<th>Drug comparison</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benitez-Rosario⁹</td>
<td>Prospective observational</td>
<td>Morphine/Methadone</td>
<td>Data on efficacy and/or side effects not examined</td>
</tr>
<tr>
<td>Mercadante¹⁰</td>
<td>Randomized controlled</td>
<td>Morphine/methadone/fentanyl</td>
<td>Data on efficacy and/or side effects not examined</td>
</tr>
<tr>
<td>Mercadante¹¹</td>
<td>Crossover, controlled</td>
<td>Fentanyl/morphine</td>
<td>Data on efficacy and/or side effects not examined</td>
</tr>
<tr>
<td>Clark¹²</td>
<td>Pooled analysis</td>
<td>Fentanyl/morphine</td>
<td>Data on efficacy and/or side effects not examined</td>
</tr>
<tr>
<td>Coluzzi¹³</td>
<td>Double blind, double-dummy, randomized crossover</td>
<td>Fentanyl/morphine</td>
<td>Data on efficacy and/or side effects not examined</td>
</tr>
<tr>
<td>Heiskanen¹⁴</td>
<td>Double-blind, randomized crossover</td>
<td>Morphine/oxycodone</td>
<td>Not combination therapy</td>
</tr>
<tr>
<td>Shinjo¹⁵</td>
<td>Case report</td>
<td>Fentanyl/morphine</td>
<td>Single case report</td>
</tr>
</tbody>
</table>
conversion ratios were unclear, and the possibility of have confounded these findings. The equianalgesic profile and fewer emetic side effects. Alternative to morphine alone, with a better analgesic nation of morphine and oxycodone may be a useful alternative to morphine alone, with a better analgesic profile and fewer emetic side effects.

Although this seems encouraging, other factors may have confounded these findings. The equianalgesic conversion ratios were unclear, and the possibility of an inadequate washout period may have been present. To provide good evidence, oxycodone and morphine should each have been titrated to analgesic effect in individual patients. Furthermore it would seem reasonable to conclude that patients who received less IR morphine would have fewer side effects.

Although as a randomized trial this would be classified as high-quality evidence (+4), the limitations in the design result in the evidence grade being decreased by 2 points to 2, or C. This would be classified as low-quality evidence.

Mercadante et al. conducted an open-label study of 14 patients who had poor pain control despite escalating opioid doses. The aim of this study was to assess the ‘effects of adding a second opioid at low dose in patients with a poor analgesic benefit after dose escalation’. This study was conducted in patients with a mean age of 61.5 years with various tumour types. Patients received either variable doses of transdermal fentanyl or oral methadone in addition to morphine. By the final week of the study (week 5) only five patients remained in the study (due to deaths or missing data). The opioid escalation index (OEI) was used to determine the effect of the addition of the second opioid. The OEI decreased after the addition of the second opioid and did not cause any significant side effects. Lower equianalgesic doses of the second opioid (20% dose equivalence) were used and clinical benefit was observed. The findings of this study are limited by lack of control, use of opioid conversion ratios which are not universally accepted, and the small number of patients who participated. This study as a non-randomized cohort study would score 2 points; however, due to limitations in study design and large losses to follow-up, it loses a point and the study would be classified as evidence quality D (very low-quality evidence).

Based on these two studies the following recommendations can be made:

- Does combination opioid therapy provide an additional analgesic benefit? Given such a key point and the present available knowledge, we give a weak recommendation for the use of combination opioid therapy (based on grade C and D evidence). This is on the basis that the desirable effects of combination opioids probably outweigh the undesirable effects based on studies included and clinical expertise.

- Does opioid combination therapy result in equivalent analgesia with fewer side effects? Given such a key point and the present available knowledge we give a weak recommendation for the use of combination opioid therapy (based on grade C evidence only). This is on the basis that the desirable effects of combination opioids probably outweigh the undesirable effects based on studies included and clinical expertise.

### Discussion

This systematic review has identified only two studies. Both studies had significant methodological problems, which resulted in these being rated as grade C and grade D evidence. As a result of this, only a weak recommendation can be used to support combination opioid therapy. This recommendation is also based on the caveat that the desirable effects of combination opioid therapy are outweighed by any disadvantages that this would confer.

Combining strong opioids in practice has implications for the patient: the number and type of tablets prescribed could affect compliance. Patients with cancer often take a multitude of medications, and combination opioid therapy could compund this. It must be highlighted that opioids are used in combination with other analgesics (e.g. paracetamol, drugs for neuropathic pain) and this ‘combination’ was not within the remit of this systematic review. Such combinations can have a synergistic analgesic response and may limit side effects.

Although there is a paucity of clinical evidence supporting combination opioid therapy in cancer, there is an urgency to optimize and refine opioid analgesic use in cancer pain. When poor pain control exists in a patient with opioid-responsive pain, the clinician is faced with a choice of opioid switching or increasing the dose of the current opioid. When opioid doses are increased rapidly there is a predisposition to increased opioid side effects and frank opioid toxicity. Opioid-induced hyperalgesia can also result; therefore, rather...
than improving pain control, high doses of opioids can lower pain thresholds and worsen an already heightened pain state.\textsuperscript{20,21}

The scientific basis for combination opioid therapy is complex and not well understood. Endogenous opioid peptides (endorphins, endorphin, enkephalins and dynorphins) have varying anatomical distributions and modulate a wide variety of physiological functions. As these natural opioid peptides have multiple roles and complex interactions at the cellular level, it is not surprising that the effects of exogenous opioids are complex.\textsuperscript{22}

Basic scientific work in combination opioid therapy is encouraging. There is now a body of work which clearly shows that multiple opioid receptors and subtypes of these receptor groups exist.\textsuperscript{7,23,24} Animal studies have taken this one step further, demonstrating that different opioids act on different sites.\textsuperscript{25} Ross et al. co-administered oxycodone and morphine to rats.\textsuperscript{25} They showed that sub-antinociceptive doses of oxycodone and morphine produced analgesic synergy compared with equivalent antinociceptive doses of these opioids in isolation. Furthermore, the opioid combination produced side effects comparable with placebo controls. Oxycodone has also been shown to behave differently from other opioid agonists through varying effects on the G protein activation inwardly rectifying potassium currents (GIRK) in animal models.\textsuperscript{26} Although opioids may act on sub-populations of opioid receptors resulting in differing analgesic effects and side effects,\textsuperscript{24} opioids do modulate opioid receptor signalling. This would suggest that a fine control mechanism exists in the opioid signalling pathways. The analgesic potency of different opioids, and side effects of these, may be due to the differences in the opioid interaction in this fine-control mechanism. This may provide a scientific rationale for the use of combination opioid therapy.

The differences between opioids observed in animal models have had variable degrees of success when replicated in human studies. In a study in patients with pancreatitis, Staahl et al.\textsuperscript{27} demonstrated that oxycodone was more potent than morphine at liberal conversion ratios, suggesting that inherent differences exist between the ways these two drugs produce analgesia.

In human studies, Grach et al. examined morphine/oxycodone combinations with healthy volunteers using the cold pressor test.\textsuperscript{28} The authors showed no apparent synergy between the opioids examined; however, this study has been criticized for its design and this may have impacted on the findings.\textsuperscript{29}

More recently, other human non-cancer studies have shown encouraging results.\textsuperscript{30} Blumenthal et al. conducted a randomized placebo-controlled, double-blind trial using morphine in conjunction with oxycodone. Patients received either oxycodone or placebo prior to surgery and the effects on post-operative morphine analgesic requirements were noted. Patients who received oxycodone and morphine combination had reduced post-operative opioid requirements and fewer side effects compared with placebo controls. This is not, however, combination opioid therapy in the context of this review. Clearly, the trajectory of pain in the peri-operative setting differs from pain with exists in the chronic state, where central sensitization and other neurobiological differences may exist.

This systematic review was limited by the extent of searching and restrictions to English language journals. The authors of the included studies were, however, contacted where no further data was available.

Currently there is a gulf between the basic scientific work which potentially supports a role for combination opioid therapy and clinical practice where combination therapy is used. The limited work in combination opioid therapy in cancer pain presented here\textsuperscript{16,18} does not yet fully support this as evidence-based practice. Appropriately designed studies (appropriately powered; clear equianalgesic conversions; quantification of side effects) are needed to allow the role of combination opioid therapy to be assessed fully.

Although combination therapy has traditionally been viewed as the concurrent use of two strong opioids for background analgesia (the viewpoint adopted for the purposes of this systematic review), there is a caveat. Rapid-onset, short-acting fentanyl preparations are being used increasingly for some types of cancer-related breakthrough pain, often on a background of a controlled-release strong opioid. This is, in effect, combination opioid therapy; however, the rationale for this approach is quite different from that discussed in this paper. When two opioids are used, each of which has a different pharmacokinetic profile, this has advantages in some situations in successfully managing stable background and rapid-onset short-duration breakthrough pain. In this situation, combination opioid therapy is used to minimize side effects of opioids used specifically for breakthrough pain.

From the data presented, a recommendation which strongly supports combination opioid therapy, in the traditional sense, would be difficult to endorse. However, when the use of a combination of opioids with different pharmacokinetic profiles (controlled-release opioid with rapid-onset opioid) is considered, things are less clear cut.

The recommendation made in this review is a weak endorsement of combination opioids in the traditional sense. The use of combination of opioids with different pharmacokinetic profiles (controlled-release opioid
with rapid-onset opioid) was not within the remit of this review.

**Conclusion**

As our understanding of opioid receptors, receptor subtypes, genetic variants, pharmacology of opioids and intra-cellular messenger systems expands, so too will our understanding of individual strong opioids. To date, basic scientific work has been limited but encouraging. The two relevant human cancer pain studies presented are of interest; however, appropriately designed studies, with sufficient attention to key details such as titration to effective doses of each opioid, rather than crude equianalgesic dose conversions, are needed.

**Funding**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Conflict of interest**

Dr Laird is supported by the European Palliative Care Research Centre. Professor Fallon has received educational grants from Pfizer and Archimedes.

**References**


25. Ross FB, Wallis SC and Smith MT. Co-administration of sub-antinociceptive doses of oxycodone and morphine


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**Appendix 1. Study summary table**

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<thead>
<tr>
<th>Title</th>
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<tr>
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<tr>
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<tr>
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<td></td>
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<tr>
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<td>Summary of results:</td>
</tr>
<tr>
<td>Side effects</td>
<td>Outcome measures:</td>
<td>Summary of results:</td>
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<tr>
<td>Narrative summary of the main results</td>
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</tr>
<tr>
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**Appendix 2. Evidence profile for each important outcome**

<table>
<thead>
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<th>KEY POINT</th>
</tr>
</thead>
</table>

| IMPORTANT OUTCOME (pain intensity or side effects) |
| N° and type of eligible studies | meta-analyses | non randomized study | randomized study |
| N | N° of patients involved |
| Study limitations | No limitations | Serious limitations | Very serious limitations |
| Consistency | No or limited inconsistency | Important inconsistency |
| Directness | No uncertainty about directness | Some uncertainty about directness | Major uncertainty about directness |
| Precision | No imprecise or sparse data | Imprecise or sparse data |
| Publication bias | No or limited probability of reporting bias | High probability of reporting bias |
| Factors that might increase quality of evidence | Large magnitude of effect | Plausible confounding, reducing a demonstrated effect | Dose-response gradient |
| Main results (narrative summary) | | |
| Quality of evidence | High quality | Moderate quality | Low quality |
| Very low quality | (+++) or (A) | (+++) or (B) | (+) or (C) |

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